A Probability Database for Decision-Analytic Models of Coronary Revascularization Procedures

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The time required to extract probabilities from medical literature is a primary reason decision analysis is not used more frequently for individual patient management decisions. Objective clinical trial information from the medical literature for one management decision was placed in a database which provided probabilities when queried. The database was tested with decision-analytic models of specific patient cases from the medical literature. Performance was assessed in terms of the ability to select trials which resembled the patients' individual characteristics, the number of trials providing probabilities for a given outcome, and the number of follow-up points available for that outcome. The timely assistance the database provides in expediting literature review and synthesis could enable the more common use of decision analysis in management decisions for individual patients.

INTRODUCTION

Decision analysis is a means for rational decision making which strives for optimal outcomes. Many examples of its application to policy, guidelines, and cost-effectiveness analyses can be found in the medical literature.[1] But decision analysis is also equally applicable to decisions in the care of individual patients. However, it is rarely used for this purpose, and the amount of time required to construct a decision-analytic model is a primary hindrance to common use. Clinicians can readily identify the intermediate clinical events and outcomes, and software allows utility assessment by individual patients within minutes, but probability assessment requires a thorough review of the literature with a detailed analytic dissection of every paper.[2,3] Even an expert in a given area can spend time measured in hours to review papers and extract the necessary probabilities.

We previously constructed a literature database to thoroughly index papers on the clinical use of thrombolytic therapy for patients with acute myocardial infarction.[4] This database was useful in decreasing the time spent on repeated reviewing of papers to extract probabilities for policy-level decision models. We have extended this work with the creation of a database which contains the actual probabilities extracted from papers it references, and we tested this database for both usefulness and timeliness in its ability to support individual patient decision-making.

Our specific goal was to create and test a probability database from the published literature on a specific patient management decision – whether a patient with multi-vessel coronary artery disease should undergo revascularization with percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass grafting (CABG). The database contains all objective information reported in the papers without synthesis or abstraction. The database allows real-time queries for probabilities which could be entered into decision-analytic models, overcoming the time-requirement obstacle to use of decision analysis. The database was tested by querying for probabilities for models for individual patient descriptions. The ability of the database to provide an adequate number of probabilities, the ability of the database to provide probabilities for different time horizons, and the ability to individualize probabilities for a specific patient were assessed.

METHODS

The first step in the creation of the probability database was to assemble the relevant literature. Four clinical trials of PTCA versus CABG to treat multi-vessel coronary artery disease have randomized between 100 and 1000 patients each.[5,6,7,8] Restriction of the literature for the database to these four trials eliminates the issues of comparing different study designs. Probabilities based on observed rates for all outcomes of either intervention were extracted. Probabilities were stratified by time to follow-up. All inclusion criteria, exclusion criteria, historical variables, medications, and angiographic data were also extracted.

The database itself was constructed with 4th Dimension, a relational database from ACI US, Inc., Cupertino, CA. The general query was: for all trials which matched the individual characteristics of a patient, retrieve probabilities for outcome x at time y. Probabilities retrieved were reported as proportions with a numerator (events) and denominator (number ran-

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domized), which is more useful to the decision-analyst than a percentage. This query would describe any probability needed for a decision-analytic model for individual patient management decisions.

The database was then tested in 3 ways. First, a general decision model from a seminal decision-analytic paper by Pauker on coronary surgery was adapted to accommodate CABG versus PTCA.[9] Pauker obtained probabilities from both experts and the medical literature; we obtained probabilities exclusively from the literature. The database was queried for all relevant probabilities as well as for several additional outcomes which would directly impact on a patient's health related quality of life. Performance was assessed in terms of the number of trials providing probabilities for a given outcome, and the number of follow-up points available for that outcome. Pauker stratified probabilities by coronary anatomy, left ventricular function, and skill of the surgical team. The probability database was tested to see if it could similarly provide these stratified probabilities.

The second test was to query the database for probabilities for three case descriptions given in Pauker's paper. Performance was assessed in terms of the number of trials providing probabilities for a given outcome, the number of follow-up points for that outcome, and the ability to individualize outcomes based on coronary anatomy and ventricular function. Additional clinical information was used to further individualize the probabilities by selecting trials which matched the patient's characteristics.

The third test was to evaluate the database's ability to individualize probabilities based on inclusion criteria, exclusion criteria, history, medications, and angiographic findings. The number of trials which could provide a probability for any variable from any of these categories was assessed, and large ranges of values for percent of patients with any variable from history, medications, or angiographic findings were specifically identified. These ranges would identify key differences among trials.

RESULTS

The inclusion criteria, exclusion criteria, historical variables, medications, and angiographic findings from each of the four trials were tabulated and served as the foundation for the database schema. Figure 1 gives the schema for the probability database. There are 3 relations: *clinical trial*, *patients*, and *outcomes*. *Clinical trial* contains citation information, the number of patients randomized, and inclusion and exclusion criteria stored as boolean fields. It holds four records, one for each clinical trial, and the field *trial name* is the key for the relation. *Patients* contains patients' histories, medications, and angiographic information for patients stratified by intervention, PTCA or CABG. The information is stored as a percentage of patients with that attribute. For example, the field diabetes holds the percentage of randomized patients who have diabetes. This relation has 8 records - one for each treatment arm of the 4 trials. The field *trial / procedure* is the key for the relation. The third relation, *outcomes*, contains the outcomes for each trial. The composite key is the set of attributes *trial / procedure*, *outcome type*, and *time*. After data entry, the relation outcomes contained 192 records. The two referential integrity constraints for the three relations are also shown in Figure 1.

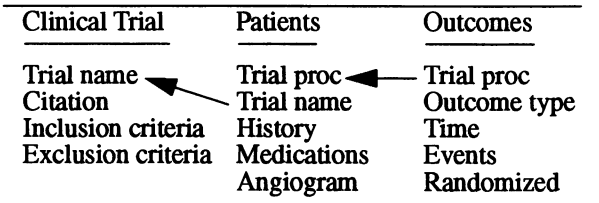

Figure 1: Schema for probability database.

All queries returned up to 8 proportions (1 from each trial arm) for any given outcome at any given time. For example, the query "what is the probability of in-hospital death" is answered with 4 proportions for CABG and 4 for PTCA. The total proportion for CABG is 15/920 (1.6%), and the total proportion for PTCA is 9/947 (1.0%). The time to compose and execute a query is measured in seconds.

The first test was to query the database for probabilities for the primary outcomes in Pauker's model: death, myocardial infarction (MI), and angina. Other outcomes that presently apply are additional interventions, specifically CABG and PTCA. Other outcomes that should be of interest to patients include employment status, physical activity, and need for and number of antianginal medications. Table 1 lists the number of trials, stratified by time, that provide a probability for these outcomes. The first number in each cell reports the number of trials reporting the outcome for patients randomized to CABG, the second number reports the number of trials reporting the outcome in patients randomized to PTCA. NA is not applicable. Two trials reported follow-up to 1 year, a third reported follow-up to 2.5 years, and a fourth reported follow-up to 3 years; the results should be

interpreted with the perspective of these follow-up points. Surprisingly, the only outcome reported by all 4 trials was death by hospital discharge. The data become sparse for other outcomes and later time points. Some outcomes, such as angina, have many variations which are reported. If an assumption is made that allows aggregation of all types of angina, then several trials can contribute probabilities to the list of probabilities that is the answer to a query.

Table 1: Number of trials by outcome and time.

Outcome	Time (years)				
	In hosp	1	2	2.5	3
Death	4,4	3,3	1,1	2,2	1,1
MI, any	3,3	2,2	0,0	1,1	1,1
Angina, any	2,2	1,1	1,1	0,0	1,1
Non-specific	0,0	0,0	1,1	0,0	0,0
CCS 2-4	1,1	1,1	0,0	0,0	1,1
CCS 3-4	0,0	1,1	1,1	0,0	0,0
Unstable	1,1	0,0	0,0	0,0	0,0
CABG	0,2	1,2	0,0	1,1	1,1
PTCA	2,1	2,2	0,0	1,1	1,1
Employed	NA	1,1	1,1	0,0	1,1
Activity	0,0	1,1	1,1	0,0	1,1
Anginal meds	0,0	2,2	1,1	0,0	1,1

Pauker individualized the probabilities by reporting probabilities stratified by coronary anatomy, left ventricular function, and skill of the surgical team. The 4 clinical trials and hence our probability database allow for stratification only by the first 2 variables. Coronary anatomy is described as the presence of a 70% stenosis and whether there is distal disease or good distal run-off. Both are included in the probability database as inclusion and exclusion criteria, respectively. The selection of these anatomic criteria limits the number of trials providing probabilities to 2 for reports of in-hospital death. A similar reduction in the number of studies is found for all other outcomes. The second variable for individualizing probabilities was the use of ejection fraction. Two trials reported normal mean ejection fractions; two trials did not report ejection fractions. The selection of normal ejection fraction in a query (roughly, where field LVEF > 50%), limits the selection similarly.

The second test of the database was to use it to find probabilities for 3 specific patient case descriptions reported in the Pauker paper. The first patient was a 45 year old male truck driver with disabling angina, occurring 4 to 5 times / day and interfering with work. The patient had 2 lesions > 70%, 1 lesion 53%, good distal run-off, and his ejection fraction was 34%. Using our probability database, the above anatomy, represented by the fields > 70% stenosis in ≥ 2 vessels (inclusion criteria) and no distal disease (exclusion criteria) eliminated 2 of the 4 trials. However, the probabilities for the three outcomes death, MI, and angina were all obtained at 1 year. This assumes that aggregate outcomes are used for MI and angina. With regard to ejection fraction, the only two trials that reported it had a normal ejection fraction, whereas this patient's was reduced. Our database does not contain trials which describe the course of patients with a low ejection fraction. However, such a patient currently may be selectively treated with surgery rather than randomization.[10] Also the time horizon is different - Pauker's probabilities were for 5 years whereas the latest follow-up point with complete probabilities in our database was 1 year. The clinical, non-angiographic information has no influence on Pauker's probabilities, but can be used with our probability database to adjust probabilities. When the probability database was queried for this information, it had no information which allowed for stratification based on age. Only one trial reported that patients age 40-49 comprised 17% of the patient population. Two others report mean ages of 55 and 61. The description of disabling angina was not useful in that it could not be identified as a discrete Canadian Cardiovascular Society (CCS) anginal class or unstable angina.

The second patient was a 35 year old male evaluated after his first myocardial infarction. He had a family history of coronary artery disease, a normal lipid profile, did not use tobacco, was not overweight, and had no symptoms. He had 2 vessel disease and an ejection fraction of 65%. Only 1 inclusion criteria, stenosis > 70% in ≥ 2 vessels, was necessary for the anatomy, and only two trials could provide patient-specific probabilities. The normal ejection fraction, when added as a criterion, limited the number of applicable trials to 1. The probability database provided probabilities for death or MI up to 1 year; probabilities for angina were not available from the publications. Further stratification was available, but the one trial left after angiographic stratification is eliminated by the absence of patients without angina. That trial did report that 2/3 of randomized patients had a smoking history, approximately 40% had a normal lipid profile, and 50% had a prior MI. In short, the database was unable to provide probabilities for the outcome angina, and it was unable to stratify based on age, lack of angina as a symptom or lack of tobacco use. It could reasonably stratify based on lipid profile and

prior myocardial infarction status.

The third patient was a 65 year old with 10 years of stable angina with 80% lesions in both the circumflex and right coronary arteries. The vessels had good distal run-off, and the EF was 55%. The anatomy and ejection fraction again limited the number of relevant trials to 1. The mean age was approximately 57, and the stable angina was not helpful without CCS classification. As with the second patient, only data on survival and MI were available, data on angina were not.

The third test of the database was to analyze the ability to individualize probabilities based on inclusion criteria, exclusion criteria, patient history, medications, and angiographic data. Table 2 contains the number of variables supported by 1, 2, 3, or 4 trials within each variable group. Most variables are supported by 1 trial, and variables supported by 3 or 4 trials are rare. Table 3 contains ranges of percentages for specific variables where the range between 2 or more trials exceeded 10%. These ranges highlight the key differences between the randomized populations and allow selection of probabilities from populations which most match a particular patient. For example, the presence of unstable angina could be used to select a trial in which 89% of randomized patients had unstable angina as opposed to trials in which 13% of randomized patients had unstable angina.

Table 2: Number of trials per clinical variable.

Variable group	Number of trials			
	1	2	3	4
Inclusion criteria	4	2	0	0
Exclusion criteria	18	5	1	1
History	20	9	1	2
Medications	8	2	0	0
Angiogram	9	1	0	2

Table 3: Variables with range greater than 10%.

Variable	Range
Angina grade 3	17–31%
Angina grade 4	25–64%
Angina unstable	13–89%
Women	11–27%
Diabetes	11–25%
Beta-blockers	32–75%
Two-vessel disease	42–85%
Three-vessel disease	15–47%

DISCUSSION

The probability database contains probabilities to support a reported general decision analysis for CABG versus PTCA. The number of probabilities decreases with longer follow-up points. When queried with three individual patients, the database could only provide probabilities, stratified by coronary anatomy and left ventricular function, for outcomes in one patient. The probability database had the ability to further stratify patients by trial inclusion and exclusion criteria, history, medications, and angiographic attributes. It identified key differences between the randomized populations in the 4 trials, and allowed selection of trials based on matching characteristics of an individual patient with those of the randomized populations. However, when these extra levels of stratification were added, probabilities of outcomes were found for approximately half of the queries.

Several reasons account for the inability to provide probabilities for all the individual patient cases. First, many trials report data in a graphical form that does not allow extraction of a precise probability. Second, the variety of outcomes reported, such as the many types of MI, requires aggregation to produce a set of probabilities for a model. Third, although trials may have similar total follow-up time reported, intermediate follow-up points within a trial are arbitrarily selected and often differ from trial to trial. Fourth, reporting of the same clinical variable varies tremendously from trial to trial. For example, continuous variables such as age are reported as means, ranges, or arbitrary stratifications. Fifth, some trials report results as intention-to-treat, others do not. Sixth, some trials report percentages rather than proportions. While intuitively it may seem that only so much information can be contained in a single publication from a clinical trial, the striking number of outcomes reported indicate that an enormous amount of information can be contained in four publications. The standardized, precise reporting of the top several outcomes could easily be accomplished. The probability database clearly illustrates problems with literature-based decision making that have culminated in proposals for clinical trial registries.[11]

The total number of randomized patients in the database should be an indication of its usefulness. The four trials collectively contained over 1700 randomized patients, which should arguably be enough patients to support any decision-analytic model. Larger databases could be constructed by accruing more trials, but realistically few patient management

decisions have this many trials on which to rest. An alternative way of finding more probabilities would be to use clinical databases which have patient level data but are considered lower in data quality.[12,13] Clinical databases allow stratification, and hence individualization of probabilities, with fewer total patients. Another alternative would be to use medical experts to supplement probabilities as Pauker did, but this approach also potentially lowers data quality. Either of these data sources could be incorporated into our probability database.

The abstraction of probabilities from various papers and their incorporation into a decision for an individual patient is informally carried out by clinicians who read papers and use the information in a paper to support clinical judgement. Certainly such informal subgroup analysis is inferior to primary outcome analysis, but patient care needs to be individualized because of real differences among patients. An abundance of validated, highly discriminatory, well-calibrated prediction rules which can individualize care do not exist. To help compensate for this deficiency, we built a probability database from medical literature to expedite the integration of disparate literature for use in decision making that clinicians undertake in the day-to-day care of patients. Insofar as the probability database does not provide perfect information, its strength is that it provides the information upon which current literature-based decision making rests. It contains all the information in the literature that a clinician can use for making decisions. Once papers are entered, it can be used repeatedly for different patients. The probability database also achieves its stated goal of supplying probabilities in a timely fashion that facilitated the use of decision analysis for individual patient decision making.

As an additional use, the probability database could facilitate meta-analysis. It allows a precise and thorough contrast of trials which can highlight differences among randomized populations in the trials. The probability database emphasizes the next step: determining whether literature applies to a given patient.

A literature-based probability database for decision-analytic models has been implemented and provides probabilities in a timely fashion. The database schema and queries are straightforward. Limitations in providing probabilities are limitations contained within the medical literature; when the database cannot provide a probability the clinician is alerted to a deficiency in the literature. The assistance it provides in expediting literature review and synthesis could enable the more common use of decision analysis in management decisions for individual patients.

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